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09/513,151	02/25/2000	Siegfried Hekimi	979-1-017	7817

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	23

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/513,151	Applicant(s) Hekimi et al
	Examiner Karen Canella	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____ .

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *21-29* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *21-29* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *22*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claim 1 has been canceled. Claims 21-29 have ben added and are under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. The specification is objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. When the specification of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application. See page 13, lines 8, 10, 12, 14, 16, 18-20, and 24-26; page 15, lines 12, 13, 21 and 29; page 16, lines 5, 12, 2 and 34; page 17, lines 2, 5-7, 11 and 28-30; page 18, lines 1, 2, 27 and 29; page 19, lines 7, 10 and 22; page 20, lines 11, 16, 17 and 21; page 21, lines 6, 12, 13, 28, 30 and 31; page 22, lines 4, 6, 8, 9, 18, 19, 22, 23, 26, 30 and 32; page 23, line 12; page 24, line 22, 33 and 35; page 25, lines 4, 10 and 13; figures 3A-C (no SEQ ID NO for the amino acid sequences); figure 3D; figure 4B; figures 5A and B (no SEQ ID NO: for P16384 and P07884); figure 7; figures 9A-B (need amino acid sequence for hgro-1p); figure 10, figures 11A-B; figure 13 (need DNA sequence); figure 14 (need DNA sequence); figure 15 (need DNA sequence) and figure 17 (need DNA sequence). Appropriate correction is required

4. Claims 23 and 24 are objected to because of the following informalities: Claim 23 is dependent upon canceled claims 1 and 2. Appropriate correction is required.

5. Claims 25-27 are objected to under 37 CFR 1.75(c) as being in improper form because a multiply dependent claim cannot serve as the basis for another multiply dependent claim. See MPEP § 608.01(n). Accordingly, claims 25-27 not been further treated on the merits.

6. Claims 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Newly added claim 23 is drawn to a fragment of the polynucleotides of SEQ ID NO:3 or a fragment of the polynucleotides encoding SEQ ID NO:3 or the complement thereof wherein said fragment can rescue at least one phenotype in a gro-1(e2400) c elegans mutant. Claim 24 is drawn to the fragment of claim 24 comprising nucleotides 1121-1210 of SEQ ID NO:3 wherein a polypeptide encoded by said fragment contains a zinc finger motif. The specification as filed disclosed that the C elegans gene of gro-1 was able to rescue the e2400 mutant (page 17, lines 11-32). Figure 9 indicates that the human version of the C elegans gene is hgro-1 (SEQ ID NO:3). The specification does not provide support for amendments substituting functions of human hgro-1 (SEQ ID NO:3) polynucleotide for functions of the C elegans gro-1(SEQ ID NO:2) as it was not demonstrated by the specification as filed that the fragments of the human hgro-1 gene can substitute for the C elegans gene in the rescue of the e2400 mutant phenotype. With regard to fragment of SEQ ID NO:3 that can suppress at least one 2400 phenotype, it is noted that the specification as originally filed teaches cosmid which can rescue the e2400 phenotype (figure 2A), the subcloning of the region common to the rescuing cosmids to pMQ2 which appeared to contain two genes, the first of which, when subcloned as pMQ3 (ZC395.7) was unable to rescue said phenotype. The specification then identified the remaining gene as gro-1 (page 9, line 12 to page 11, line 4). The specification did not contemplate a subregion of gro-1 or hgro-1 that would rescue the e2400 phenotype. This is insufficient support for amendments drawn to fragments which can rescue the e2400 phenotype. Further, there is no support in the specification for the suppression of specific characteristic of the 2400 phenotype versus the suppression of all the characteristics. The specification as filed does not provide enablement for the use of that different elements of the gro-1 gene for the suppression of different 2400 phenotypes. Further, newly added claims 23 and 24 are dependent on the complement of

SEQ ID NO:3 or the complement of the polynucleotides encoding the polypeptide of SEQ ID NO:3, and the specification as filed provides no support for an anti-sense construct of gro-1 or hgro-1 which can rescue the phenotype of the e2400 mutant.

7. Claims 21-24 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility. Upon review and reconsideration, the utility rejection is being re-applied to the instant invention. Claims 21 and 22 are directed to an isolated polynucleotide comprising a nucleotide sequence of SEQ ID NO:3 and isolated polynucleotides encoding the polypeptide encoded by SEQ ID NO:3. Claim 23 is drawn to a fragment of said polynucleotides, wherein said fragment can rescue at least one phenotype in a gro-1 (e2400) C elegans mutant. Claim 24 is drawn to the fragment of claim 23 comprising nucleotides 1121-1210, wherein a polypeptide encoded by said fragment contains a zinc finger motif. The specification teaches that SEQ ID NO:3 is the human homolog of the C elegans gro-1 regulates disparate physiological and metabolic processes in C elegans (page 19, lines 6-15) and is homologous to DMAPP transferase of bacteria which catalyzes the modification of adenosine 37 in tRNAs having an anticodon beginning with U (page 14, lines 29-35). The specification teaches that sorting motifs were not evident in SEQ ID NO:3 (page 16, lines 23) In a previous response, Applicants have submitted the reference by Golovko et al (Gene, 2000, Vol. 258, pp. 85-93) as a means for establishing a utility for the claims hgro-1 of SEQ ID NO:3. A search of the polynucleotide databases reveals that the instant hgro-1 encodes that same amino acid sequence as disclosed by Golovko et al for human isopentenyl transferase, with the exception of a 26-mer peptide insert, a substitution of His for Tyr at residue 414 and a substitution of Gly for Glu at position 420. SEQ ID NO:3 contains motifs representative of the tRNA delta(2)isopentenyl transferases and therefore it is reasonable to assume that SEQ ID NO:3 has the same enzymatic activity as the prior art isopentenyl transferases in the modification of cytoplasmic and mitochondrial tRNAs to place an isopentenyl moiety on position 37. The

specification states that the C elegans and bacterial homologs of hgro-1, gro-1 and miaA "increase the rate of spontaneous mutations, which is generally suggestive of a role in DNA metabolism, and can be related to the observation that methylation is linked to spontaneous mutagenesis, genome instability and cancer " (page 21, line 6-11). The specification states that gro-1 can induce an epigenetic state which is not altered by subsequent growth (page 20, lines 25-27). However, the specification fails to assert a specific, substantial and credible utility for SEQ ID NO:3. It is noted that the reference of Golovko et al, also fails to teach a utility for the disclosed isopentenyl transferase as well. Golovko et al remarks on the presence of a single Zn-finger motif (page 92, second full paragraph) notes that the human sequence could partially complement the loss-of-suppression phenotype of MT-8 (pages 87-92, section 3.2). The teachings of Golovko et al do not represent a specific and substantial utility for the human isopentenyl transferase, therefore, the instant isopentenyl transferase cannot rely on being a member in the class of human isopentenyl transferases for utility. The speculation that the instant isopentenyl transferase is related to spontaneous mutagenesis, gnome stability and cancer or epigenetic control of gene expression is not a credible utility without a specific enablement set forth in the specification. The specification fails to provide support for the notion that the instant isopentenyl transferase, or an altered form thereof, can be passed from a mammalian mother to her offspring, and that this altered form influences the expression of genes in said offspring and is not altered by somatic growth. The specification fails to identify a pattern of gene expression in an offspring which is controlled by the instant SEQ ID NO:3 or an altered form thereof. The specification fails to teach the correlation with a specific inherited disease and the presence or absence of SEQ ID NO:3, or an altered form thereof. The specification fails to teach a correlation between a human phenotype and the presence or absence of SEQ ID NO:3, or altered form thereof. With regard to the comparison between isopentenyl transferase activity and methylation activity, it is note that although egg cells comprises an established methylase activity from the mother, this activity rapidly disappears and is replaced by maintenance methylation activity in the cells of developing

tissues (Alberts et al, page 584, second full paragraph). It is reasonable to conclude that the maintenance methylation activity is specific to the offspring and not maternal in origin. Further, it is noted that DNA methylation plays a more subsidiary part in cell diversification because a highly methylated gene can be activated by regulatory proteins regardless of methylation status (Alberts page 585, first two full paragraphs). With regard to the argument that methylation is related to spontaneous mutations, gnome instability and cancer it is noted that inactive DNA is often highly methylated in vertebrates; however, inactive DNA is not repaired as quickly as actively transcribed DNA which has lost methyl groups, due to the removal of the DNA lesion from transcribed strands by means of Pol II which is part of the transcription complex (Smerdon et al, In: DNA Damage and Repair (monograph), Vol. II, pages 210-212, especially page 211, last full paragraph). Ushijima et al (1997, PNAS, Vol. 94, pp. 2284-2289) disclose that alterations in the distribution of methyl groups occurs in mouse liver tumors and that clones of DNA comprising areas of hyper methylated DNA versus hypo methylated DNA can be isolated. It is noted that the instant specification does not provide any objective evidence that the presence or absence of an altered level or form of SEQ ID NO:3 is associated with the neoplastic state. Jones et al (PNAS, 1997, Vol. 94, pp. 2103-2105, page 2103, second column, second full paragraph) point out the contradictory evidence which exists associating methylation status and cancer. Jones et al teach that in experiments wherein CpG methylation rich sequences versus CpG hypo methylated sequences are transfected into colon cancer cells, only cell which have ms-match repair capability are able to express the highly methylated DNA. Jones et al point out that this is in contrast to Fineberg et al (page 2104, first column, first full paragraph) who teach that colon tumors often have reduced methylation content relative to normal tissues and Laird et al who teach that lowering the level of maintenance methylase resulted in a lower level of pre-neoplastic lesions in mice. Jones et al notes that although methylated plasmids are retained with higher efficiency than unmethylated plasmids, this does not serve as a bassi for presuming that methylation enhances genomic stability because hyper methylation rather than hypo methylation precedes allelic loss in

neural tumors. Jones et al conclude that until the relationship between the de novo methylase, the maintenance methylase and the demethylase is understood, it will not be possible to resolve the apparent discrepancies with regard to methylation status and cancer. Jones et al states "because methylation presumably plays multiple roles in carcinogenesis, it may be that different pathways are selected with differing degrees of penetration in diverse situations"(page 2104, second column, first full paragraph). Thus, it appears from the work of Ushijima et al that methylation of a specific area of DNA or a specific group of genes is more important than the overall level of DNA methylation in tumors. Given the contradictions in the published literature, it can be concluded that the state of the art with regard to DNA methylation and its relationship to cancer is unreliable. Further, given the lack of any evidence that the instant isopentenly transferase of SEQ ID NO:3 acts epigenetically to control gene expression in mammalian cells , and the lack of any correlation between the level or form of SEQ ID NO:3 with specific disease or cancerous state, it is concluded that the instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a credible, specific and substantial utility. The disclosure of SEQ ID NO:3 is simply a starting point for further research and investigation into potential practical uses of the claimed nucleic acids. It is note that in a 2001 publication, the instant inventor fails to disclose the functional significance of hgro-1 in humans (Genetics, 2001, Vol. 159, pp. 147-157). "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner v. Manson, 148 USPQ at 696.

8. Claims 21-24 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claim 22 is rejected under 35 U.S.C. 102(b) as being anticipated by Hudson (Accession number G24438, May 31, 1996). Claim 22 is drawn in part to a complement of a polynucleotide that encodes a polypeptide encoded by SEQ ID NO:3. Hudson et al discloses human STS WI-12773 which is a complement to residues 1778-2029 of SEQ ID NO:3.

11. Claims 23 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonaldo et al (Genome Research, 1996, Vol. 6(9):791-806) as evidence by accession number BM721352.

Claim 23 is drawn to fragments of the polynucleotides which encode the polypeptide encoded by SEQ ID NO:3, wherein said fragment can rescue at least one phenotype in a gro-1 (e2400) mutant. Claim 24 specifies that these fragments must comprises residues 112101210 of SEQ ID NO:3 which is the zinc finger motif. Bonaldo et al disclose Homo sapiens cDNA clone UI-E-E01 which comprises residues 1121-1210 of SEQ ID NO:3. Bonaldo et al do not disclose that said clone encodes a fragment comprising a zinc finger motif, but said motif is inherent within residues 74-163 of the disclosed polynucleotide. Bonaldo et al do not disclose that said fragment can rescue the e2400 phenotype, but the disclosed polynucleotide meets the required limitation of comprising residues 1121-1210 of SEQ ID NO:3, therefore it is reasonable to assume that it would have the same inherent properties of rescuing the e2400 phenotype as claimed.

12. All rejejctions and objections as set forth in Paper no. 18 are withdrawn.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
April 30, 2003